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Immunonutrition—Fact, Fancy or Folly?

Joe Krenitsky

Research into specific nutritional components that may favorably affect immune function has stimulated the development of commercial enteral nutrition products designed to improve the outcomes of hospitalized patients. Randomized trials of these "Immunonutrition" formulas have yielded tantalizing, but sometimes conflicting, results. Qualitative and systematic reviews of these products have not resulted in consistent conclusions regarding appropriate use in all patient populations. An evaluation of the methods and limitations of the key studies of immunonutrition formulas allows an understanding of patient populations who may benefit from these formulas and the knowledge gaps that still exist.

INTRODUCTION

The link between malnutrition and impaired immune function is well described (1,2). In fact, the "immunoparesis" caused by malnutrition is so predictable that reduced lymphocyte count and impaired response to antigens were traditionally used as components of nutrition screening (3). The conventional role of nutrition support in immune function has been limited to preventing or reversing immunosuppression related to malnutrition. However, research into specific nutritional components that may favorably affect immune function has stimulated the development of commercial enteral products designed to improve the outcomes of hospitalized patients by reducing infections. This article will examine the data generated from these controlled trials in order to understand the current status of these formulas. The review will focus primarily on outcome data from prospective, randomized studies in adult patients with commercial enteral immunonutrition (IMN) formulas, and not delve deeply into studies of single supplemented nutrients or studies that only document changes in biochemical or immunological tests. It is not a meta-analysis, or an exhaustive evaluation of every study, but is intended to cover the pertinent studies to assist clinical decision-making in an evidence-based manner.

Joe Krenitsky, M.S., R.D., Nutrition Support Specialist, Digestive Health Center of Excellence, University of Virginia Health System, Charlottesville, VA.

WHAT IS IMMUNONUTRITION?

The term "Immunonutrition" has been popularized to describe enteral feeding formulas that have been supplemented with some combination of the amino acids arginine and/or glutamine, omega-3 predominant oils (often marine oils), nucleic acids, and additional "antioxidant" vitamins and minerals. Animal models and human studies have suggested that the individual components have beneficial (or potentially beneficial) effects on immune function.

In an ideal situation a number of human studies would have been completed with progressive addition of the immune modulating nutrients to determine which nutrients are necessary and the ideal nutrient amounts, ***prior*** to introduction of commercial formulas. Considering the exceptional expense and time required for such trials, the approach to IMN product development has been more pragmatic. Manufacturers have used data from animal trials and small human studies to combine nutrients in different amounts in several different IMN formulas.

COMPONENTS OF IMMUNONUTRITION

Arginine

Arginine has been classified as a conditionally essential amino acid because endogenous production may be inadequate during periods of growth, illness or injury (4). Studies have demonstrated that supplemental arginine can improve nitrogen balance, increase indices of T-cell immune function, and increase collagen deposition in wound grafts (4,5). Postoperative oncology patients who received supplemental arginine (25 gm/day) demonstrated significant improvement in T-lymphocyte response and percentage of T-cells (CD-4 phenotype) compared to patients randomized to receive isonitrogenous placebo (5). Arginine serves as a substrate for production of nitric oxide. Arginase and nitric oxide synthase compete for arginine as a substrate, and the metabolic products of these enzymes are important modulators of T-cell function. Arginine also functions as a secretagogue, increasing growth hormone, insulin-like growth factor-1 and prolactin levels.

Glutamine

Glutamine is an amino acid that serves as an oxidative fuel for rapidly dividing cells in the body, including enterocytes and colonocytes (6). Glutamine also serves as a nitrogen shuttle and gluconeogenic precursor in the Cori cycle, and as a primary component of the antioxidant glutathione. Glutamine has been studied as a single additive to enteral or parenteral nutrition (PN), and also as part of a mixture with other nutrients in "immunonutrition" enteral formulas.

Glutamine is not present in PN solutions because free glutamine is not stable in solution. Supplemental glutamine added to PN has been studied in bone marrow transplant patients randomized to PN with glutamine or an isonitrogenous control solution. Those patients who received the PN supplemented with glutamine had a decreased incidence of infections and a shorter hospital stay compared to the control group (7). In contrast to PN, most enteral feeding formulas contain some glutamine as part of the protein.

Omega-3 Fatty Acids

Fish oils are rich in the omega-3 fatty acids eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids compete with arachadonic acid (omega-6) and thus influence production of prostaglandins, leukotrienes, thromboxanes and prostacyclins. The addition of EPA and DHA to enteral nutrition products results in a reduction of proinflammatory mediators in stressed patients (8). Early research in an animal model for burns suggested that the addition of fish oils rich in omega-3 fatty acids to feedings could reduce infectious complications (9). However, increasing omega-3 fats beyond a certain point appeared to actually increase mortality in an animal model of peritonitis (10). Marine sources of omega-3 fats can increase the generation of free radicals and increase apparent antioxidant requirements (11). Animal studies suggest the level of antioxidant support during omega-3 fatty acid supplementation **is** of consequence. However, human outcome data does not exist to guide formulation of the ideal ratio of omega-3/antioxidants in a critically ill population.

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Table 1.
Immunonutrition Products and Comparison (per 1000 kcal)

Product	*Kcal/mL*	*Arginine (gm)*	*EPA/DHA (gm)*	*Glutamine (gm)*	*Nucleotides (gm)*
AlitraQ[a]	1.0	4.4	0	15.5	0
Crucial[c]	1.5	10	3.6	0	0
Immun-Aid[d]	1.0	14	0	12	1.0
Impact[b]	1.0	12.5	1.7	0	1.2
Impact 1.5[b]	1.5	12.5	1.5	0	1.2
Optimental[a]	1.0	5.5	3.26	0	0
Perative[a]	1.3	6	0	0	0
Pivot 1.5[a]	1.5	8.6	2.6	0	0
Stresson Multi-fibre[c]	1.25	7.12	0.88	10.4	0

[a]Ross Products 800-227-5767 www.ross.com
[b]Novartis Nutrition 800-333-3785 www.novartisnutrition.com/us/home
[c]Nestle Clinical Nutrition 800-422-2752 www.nestleclinicalnutrition.com
[d]Product discontinued
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Nucleotides

The normal diet provides 1–2 grams of nucleotides per day from animal proteins, peas, beans, and milk. However, most enteral feeding formulas are devoid of preformed nucleotides. Animals maintained on a nucleotide-free diet demonstrate an impaired immune response and decreased survival in response to an infectious challenge compared to animals that received an exogenous source of nucleotides in their diet (12,13). There are no human trials that have investigated the effect of supplementing nucleotides (as a single additive) to patients maintained on standard enteral feedings. Some IMN formulas provide a source of nucleotides, while other formulas do not.

Antioxidants

One component of IMN formulas that should not be overlooked is the increased amounts of vitamin E, vitamin C, selenium and zinc. There are increasing data that antioxidant vitamins and minerals may positively influence outcome in critically ill patients (14,15). A recent study in critically ill surgical patients reported that patients who received vitamin C and E supplements had reduced pulmonary morbidity (RR = 0.81, CI = 0.60–1.1) as well as a significantly reduced incidence of multi-organ failure (RR = 0.43, CI = 0.19–0.96) (15). It is worthy of notice that the randomized trials of IMN formulas do not control equally for antioxidant levels. In some studies, the control formulas had significantly less micronutrient content (16,17). However, in at least one of the trials in which IMN formulas did not reduce infectious complications, the control formula had vitamin/mineral content significantly greater than the IMN formula (18).

RANDOMIZED TRIALS

There are over 30 studies of IMN enteral formulas and at least 3 meta-analyses (19,20,21). Over 2,500 patients have been enrolled in the randomized trials. However, the topic of appropriate use (if any) of IMN formulas remains highly controversial.

The difficulty in arriving at a clear and universal opinion on IMN formulas stems from the methodolog-

Protein (gm)	*% Fat Calories*	*Vitamin C (mg)*	*Vitamin E (IU)*	*Zinc (mg)*	*Selenium (mcg)*
52.5	13.2%	200	30	20	50
62.5	39%	667	66.7	24	66.7
37	20%	60	50	25	100
56	25%	80	60	15	100
56	40%	64	48	12	80
51.3	25%	215	215	16	50
51.3	25%	200	31	15	47
62.5	30%	200	166.7	17	47
60	30%	104	69	8	113

ical limitations of many of the trials, differences in the formulas tested, and different endpoints of the studies. The earliest studies of IMN formulas reported enticing positive outcomes in the IMN groups, however, these studies were criticized because the control groups received a feeding formula with a much lower protein content that was inappropriate for the study population (23,35). Recent studies have used more appropriate controls, but the results have varied in different studies and in different populations. To appreciate the state of the science behind these products requires close attention to the materials and methods of the key studies.

There are several IMN formulas currently marketed, each formula having a different composition. The amount of arginine in several of the IMN formulas is significantly different. Some formulas contain arginine, marine oils and nucleotides, while others contain only arginine and marine oils, and some contain arginine and glutamine, but no marine oils (Table 1).

One of the limitations of these studies is that a different type of "control" formula was used in each study. In one study, a control formula was carefully constructed to match the IMN formula in every detail except the "immune" nutrients (22). In other studies, the control formula contained a higher percentage of fat and significantly lower levels of antioxidant vitamins and minerals (16,17). Yet another used a control formula with similar fat calories, greater protein, and significantly increased levels of antioxidants in the control formula, compared to the IMN formula (18). An additional factor that complicates analysis of the results of the randomized trials of IMN formulas is the amount of nutrition that is actually received by the patient. Enteral feeding studies have the unique complication that only a minority of the subjects received the full "dose" of the product being evaluated (see Table 2 for additional details).

Studies in Trauma Patients

A large study in trauma patients reported a reduction in abdominal abscesses and multi-organ failure with IMN formulas compared to control formula (23). However, the control feeding used in this study provided significantly less protein than the IMN formula. Since then,

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Table 2.
Selected Immunonutrition Studies

Study	*Population*	*N*	*Product*	*Control*	*Amount nutrition received*	*Outcome: Infection*
Atkinson	Mixed medical/surgical	390	Impact	Isocaloric Isonitrogenous Isomicronutrient	14 Kcals/Kg	Not Reported
Bower	Mixed trauma, surgery, sepsis	296	Impact	Isocaloric, Not Isonitrogenous	16 Kcals/Kg	Not different (intention to treat)
Kudsk	Trauma	35	Immun-Aid	Isonitrogenous, Isocaloric	18 Kcals/Kg	Significantly reduced
Galban	Medical	176	Impact	Isonitrogenous Not Isocaloric	20 Kcals/Kg	Significantly reduced
Saffle	Burn	50	Impact	Control received more protein, 4X more vitamin C	26 Kcals/Kg	Not different
Kieft	Mixed, Trauma, Surgery, Medical (APACHE II 16)	597	Stresson Multi Fibre	Isocaloric, Not Isonitrogenous	Approx. 1300 Kcals/day (65% of required)	Not different
Senkal	Postoperative GI malignancy	154	Impact	Isocaloric, Isonitrogenous, Isomicronutrient	25 Kcals/Kg planned (actual amount not presented)	Infections not reported separately
Mendez	Trauma	43	Ross Experimental	Isonitrogenous Isocaloric Micronutrients not reported	26.5 Kcals/Kg	No significant difference
Heslin	Postoperative, GI Malignancy	195	Impact	IV fluids	8 Kcals/Kg (30% of goal)	Not Different

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two randomized studies that have compared IMN to an isonitrogenous control formula have been reported in trauma patients (24,25). One study of 35 patients used IMN containing 14 gm of arginine and 12 gm of glutamine per 1000 calories (24). The investigators reported significantly reduced intra-abdominal abscess, length-of-stay, and hospital costs compared to control formula.

The second study in 43 patients used IMN containing 5.1 gm arginine and 14.6 gm glutamine per 1000 calories (25). The authors reported no significant difference in infectious complications or mortality, but reported that the IMN group had a trend towards an increased time on the ventilator and length of stay. It should be noted that bias may have been introduced

Outcome: Mortality	*Outcome: Other*	*LOS*	*TPN?*	*Comments*
Numerically increased	Numerically increased	Not significantly different	No	Double-blind
Numerically increased	Fed septic patients had sig. reduced infections, bacteremias	Not different (intention to treat)	No	Septic patients who received feedings had increased mortality.
Not different	Reduced hospital costs	Significantly decreased	None	Small groups, Product no longer commercially available.
Significantly reduced	N/A	ICU LOS not different	No	Control Group Received significantly more calories. Not double-blind
Not different	N/A	Not different	No	Small Groups, Control Received more micronutrients
Not different	Organ dysfunction – Not different	Not different	Not reported	Low Arginine Formulation
Not significantly different	Costs reduced	Not different	No	Required 5 days to reach full feeds. Complications after day 5 reduced.
No significant difference.	N/A	Numerically greater in immune group.	No	Small groups, more ARDS in experimental group prior to receiving feeding.
Not different	N/A	Not different	No	Patients received only 30% of goal from tube feeding.

into this study during the randomization of a relatively small number of patients, as there was an unequal distribution of patients with acute respiratory distress syndrome (ARDS) between the groups. Prior to the initiation of feedings, ARDS was diagnosed in 31% of the IMN group, but only in 14% of the control group. The difference in the number of ARDS cases between the groups suggests an unequal distribution of patients during randomization and may account for the longer time on the ventilator and in the hospital. The difference in the results of these two studies also raises the important point that the amount of added nutrients (arginine) may affect the efficacy of IMN. The IMN

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formula used in the positive study by Kudsk had a higher arginine content than any other IMN product (24). Of note, the high-arginine IMN tested in the study by Kudsk (Immune-Aid) is no longer commercially available. The small numbers of patients in each of these studies makes it difficult to make strong conclusions regarding the efficacy of IMN in trauma patients. There is a need for an adequately powered study before the additional expense of IMN can be justified in trauma patients.

Several studies have investigated the effect of glutamine alone in trauma patients (26–28). The first study randomized 72 patients with an Injury Severity Score of 20 or more to receive a glutamine-enriched enteral feeding (30 gm glutamine/100 gms protein), versus an isonitrogenous, isocaloric control feeding for at least 5 days (26). The glutamine group had a significant reduction in pneumonia (17% vs 45%, $p < 0.02$), bacteremia (7% vs 42%, $p < 0.005$) and sepsis (3% vs 26%, $p < 0.02$). There are concerns that the control group had an unusually high incidence of pneumonia and bacteremia within the short span of this study, and the study did not investigate mortality.

A second trial of glutamine alone was a double-blind study in 363 general ICU patients randomized to receive 20 gm glutamine or glycine to their tube feeding formula for a median of 10 days (27). There were no significant differences in infections, severe sepsis, mortality, or antimicrobial therapy. A subgroup analysis of 184 (48%) trauma patients also demonstrated no difference in outcomes.

A recent quasi-randomized and unblinded trial of 185 surgical and trauma patients reported no reductions in infectious complications or mortality with supplemental glutamine. The results instead suggest a slight trend towards increased mortality when glutamine was added to standard high-protein or to IMN tube feeding when compared to a standard high-protein feeding with protein powder, but the study was stopped prior to obtaining adequate numbers to adequately evaluate this result (28).

Burn Injury

Surprisingly, there are few studies of IMN in burn patients considering that one of the inspirations for the first IMN formula was the Shriners burn formula. One study randomized 50 burn patients to receive either IMN or a standard high protein, enteral feeding (18). The investigators reported that there were no significant differences in infectious complications, length of stay or mortality between the two groups. Some reviews have disregarded this study because the control group received more protein and suggested that the control formula contained immunonutrients (29,30). However, the control formula was a standard, high-protein formula that did not contain additional (beyond what was in the protein) arginine, glutamine, fish oils or nucleotides. The fat content was also modest (30% of total calories), and fat sources were canola oil and medium-chain triglycerides, providing low-levels of omega-6 fatty acids. The control feeding did have substantially higher amounts of several micronutrients, including vitamin C, zinc, and vitamin A, but it should not be considered an IMN formula simply because it contains monounsaturated fats and additional micronutrients.

Several groups have reported decreased length of stay and improved wound healing with glutamine added to enteral nutrition in patients with burn injury (31–33). One group reported a decrease in infections and mortality with enteral glutamine supplements compared to control in 41 burn patients (31). However, there was 10% more inhalation injury in the control group in this study. The difference in inhalation injury was not statistically significant, but the total group sizes were small, and inhalation injury has a potent effect on outcome in this population. Other researchers (32,33) have not reported changes in infectious complications but have noted decreased length of hospitalization and faster wound healing in the glutamine supplemented groups. In total, the results of these studies suggest that larger trials of enteral glutamine supplementation in burn patients are desirable. A recent meta-analysis of glutamine suggests that there may be a dose-dependent effect of glutamine, and that parenteral glutamine may have even greater benefit than enteral glutamine in the burn population (34).

Surgery

The earliest studies of IMN in surgical patients reported significant reductions in infectious complica-

tions and length of stay compared to standard enteral feedings (35). However, analogous to the early trauma IMN investigations, these studies were criticized for providing control feedings with significantly less protein to a population with an increased protein requirement. Subsequently, several double-blind randomized studies with IMN have been published using isocaloric and isonitrogenous control feedings. One study of 206 patients with gastrointestinal malignancies (colorectal, stomach, pancreas) compared IMN with a control feeding taken orally for 7 days prior to their procedure, and then provided postoperatively via jejunal tube for 7 days (36). The investigators reported a significant reduction in infectious complications (14% vs 30%, p = < 0.09) and length of stay (11.1 vs 12.9 days, p < 0.01). One factor that sets this trial apart from many other IMN studies is the way that the patients received the IMN formula: within 6 hours post-op, for a longer period of time, and finally, a greater percentage of nutrition needs were met.

A second study randomized 164 patients with upper GI cancer to receive postoperative jejunostomy feedings with IMN or control feeding (37). This trial started feedings at 20 mL/hr 12–24 hours postoperatively, and advanced to goal rate by postoperative day 5. The authors reported that overall complications, and early postoperative complications (up to day 5) were similar between groups, but that late phase complications (after day 5) were significantly less in the IMN group (5 IMN vs 13 control, p < 0.05). This study has been categorized as a negative study in some reviews that mention only the lack of significance overall, but the results demonstrate a significant reduction in complications once patients actually received reasonable amounts of the IMN formula.

Two studies have compared IMN versus no nutrition support in patients receiving surgery for GI cancer. The first study randomized 195 patients to receive either IMN via jejunostomy or only conventional IV fluids after surgery until the patients were able to resume oral intake (38). The authors reported no difference in infections, mortality or length of stay between the two groups. The authors report that the IMN group received 60% of their nutrition goals, but it is essential to realize that the IMN formula provided only 40% of the nutrition needs for 2 days (dextrose in IV fluids provided the additional calories). The remainder of the study days the IMN group received 15%–30% of their nutrition needs from the IMN formula.

There is a valid concern that the provision of any nutrition support may impart only negative consequences when it is provided to patients who are not malnourished (39). One study compared the effects of preoperative IMN with no nutrition support in 305 patients scheduled for elective GI cancer surgery (40). Patients with <10% weight loss were randomized to one of three groups:

1. Oral IMN (1L/day) for 5 days prior to surgery, with no post-op nutrition support,
2. Oral IMN for 5 days, with postoperative jejunal IMN, or
3. No specialized nutrition support before or after surgery.

The investigators reported a significant reduction in postoperative infections and hospital length of stay in both IMN groups compared to those who did not receive nutrition support.

Critical Illness

The subject of IMN in the critically ill patient has been a source of controversy and the topic continues to provoke passionate debates from letters to the editor to nutrition support listservs. The first multicenter trial of IMN did not demonstrate significant advantages over the control feeding on an intention to treat basis, however, the study did identify a subgroup of patients with improved outcomes (17). Patients with sepsis who received more than minimal feeding (821 mL/day), had a significant reduction in length of stay and acquired infections compared to the control group. This study, like a number of the earlier studies, was criticized because the control feeding contained insufficient protein. The IMN group had numerically greater mortality, which was not statistically different from the control group on an intent to treat basis.

Atkinson, et al studied 398 heterogeneous ICU patients randomized to receive IMN or an isonitrogenous, isocaloric control formula (22). This study is one of the few investigations that ensured that the control formula also contained identical vitamins and minerals

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as the IMN formula. On an intention to treat basis, there were no significant differences in any outcome measure between the groups. However, in the 101 patients who successfully received early enteral nutrition (at least 2.5 L of formula in the first 72 hours), there was a significant reduction in the requirement for mechanical ventilation and hospital length of stay. The authors did not report infectious complications in this study. There was no significant difference in mortality between the two groups, but similar to the earlier study, there were numerically more deaths in the IMN group. When the decreased length of stay from mortality was taken into account, the shortened length of stay in the IMN group was no longer statistically significant. One factor that limits the conclusions that can be made from this study is that even the patients defined as "successful" early feeders, only received, on average, 833 calories per day.

A third trial was completed in 181 patients who were septic at randomization (16). The patients received the same IMN formula (Impact, Novartis) as the previous two studies compared to an isonitrogenous isocaloric control feeding. The authors reported that the IMN group had significantly decreased mortality, decreased bacteremias, and a significant reduction in the number of patients with more than one nosocomial infection. One of the important factors to note in this study is that patients received a significant amount of IMN—an average of 20 Kcals/kg in the first 7 days. However, this was not a double-blind trial, and as a result, the findings of this study have not been incorporated into some meta-analysis.

In some reviews (41,42) the Galban study has been offered as evidence that only those patients with an Acute Physiology Score (APACHE II) of ≤15 will benefit from IMN because the effect was more prominent in that subgroup. However, no subgroup had significantly increased mortality from IMN, in fact, the mortality of those receiving IMN was numerically less in all subgroups up to APACHE II score of 25. The group size of those patients with an APACHE II score over 25 was only 19 patients, with 4 deaths in the control, and 5 in the IMN, so it is not possible to make any strong conclusions about mortality in this subgroup. Considering the entire study population as a whole, which does have adequate power to draw conclusions, the use of IMN significantly decreased mortality.

Recently a fourth study was published in a heterogeneous group of 597 ICU patients with a different IMN formula (Stresson Multi Fibre) than the previous 3 studies (43). The control group received an isocaloric feeding that was lower in protein then the IMN formula (control = 16% protein, IMN = 24% protein). The average caloric intake of the 473 patients who completed the protocol was 1330 Kcals/day. There were no significant differences in infectious complications, mortality, length of stay, or days on ventilator in either the intention to treat (n = 597), or in those who completed the protocol (n = 473). The potential limitation of this study was that the entry criteria required patients to receive enteral nutrition for only 2 days. The authors do not provide information regarding how long patients actually received enteral feeding, or how many patients received only short-term feeding. It is possible that the study protocol could have allowed some patients to receive IMN for a very short period. One of the most notable differences between this study and the previous 3 is that the IMN formula in the previous 3 studies provided more than 40% more arginine than Stresson Multi-fibre. This is a critical consideration because a meta-analysis of IMN found that those IMN studies with lower amounts of arginine actually demonstrated increased mortality when the results were pooled in a meta-analysis (19). In contrast, the same meta-analysis revealed that those studies done with IMN that contained greater amounts of arginine demonstrated significantly reduced infections and no significant increase in mortality. A recent study that compared IMN with PN in patients with sepsis would seem to confirm these results (44). The enteral IMN provided less than 50% of arginine than the formula in the Bower, Atkinson and Galbon studies (16,17,22). The investigators stopped recruitment into the trial because mortality in the low-arginine IMN group was significantly higher than that of the PN group.

DISCUSSION

It is more than 15 years since the introduction of commercial IMN products and the publication of the first IMN studies. There are now a large number of randomized trials and at least 3 meta-analyses, but there remains a lack of consensus on the issue of routine use

of IMN formulas in many patient populations. Opinions appear to be polarized. Some reviewers note the lack of any outcome benefit in the intention to treat analysis, and stress the increased mortality when studies of all arginine-containing formulas are analyzed together. Other experts have highlighted the positive outcomes in populations who actually received adequate amounts of IMN, and note the decrease in infections and the decreased (or unchanged) mortality in studies that have used high-arginine formulas. Some of the divergence in opinion regarding appropriate indications for IMN is caused by the inherent limitations in each of the studies that have been completed. Several of the key limitations of the available data should be considered before forming any "take-home" recommendations regarding the use of IMN.

Study Size, Volume of Formula Received and Length of Study Period

Most of the IMN studies suffer from the limitation of very small sample size, and thus inadequate power, to adequately address outcomes such as mortality. This issue of small sample size is crucial in diverse populations such as those of critically ill patients with the myriad of variables affecting outcomes. A comparison to studies in other areas of critical care illustrates the relatively small size of even the largest IMN study. A recent editorial regarding the lack of an outcome advantage in a study of sepsis and activated protein C commented that, "it was not possible to make meaningful statistical comparisons regarding mortality in a group because the population of 324 patients was too small" (45). This is a much larger study than most IMN studies, and studies of medications are generally not hindered by issues such as "high residuals" (let alone the varying definitions of same) or perceived feeding intolerance. There are few other medical specialties that must contend with interpretation of data where the experimental group receives only a portion or varying amounts of the agent being tested. Additionally, it should be remembered that some IMN trials have included data from patients fed for only a few days. The failure of a nutritional product to affect mortality in a critically ill patient when administered for 48 hours does not necessarily rule out the possibility of positive outcome changes when provided to patients at risk over an extended hospital stay. In a postoperative population, there was no outcome difference between the groups during the first five days when feedings were started slowly and advanced over several days (37). After 5 days, when the groups were receiving reasonable amounts of the products tested, there was a significant reduction in infectious complications in the IMN group. In the general ICU population there is no study that has had enough patients, who actually received sufficient feeding, for a reasonable length of time, to allow strong conclusions to be reached about mortality. Most authorities would agree that larger, well-controlled studies are desirable.

Composition of Control Feedings

One other factor that makes interpretation of the current research difficult is the fact that the studies have used various types of control formulas. Very few studies have used a feeding formula that is the same in every respect except for the selected "immunonutrients." Some control groups have received control feedings with higher fat content (16,17), while others have used control feedings that are lower in fat (28). Some control groups have received substantially increased amounts of vitamins and minerals that function as, or support, antioxidants (18,28). There are data to suggest that antioxidant micronutrients may improve outcome in critically ill patients (14,15). One of the key studies where IMN has demonstrated significant improvements in outcome used a control formula with a higher fat and substantially reduced vitamin/mineral content (16). In one study where all of the micronutrients and fat content were matched between the control and IMN formula, there was only a trend towards reduced length of stay in the IMN group (22). Two studies where IMN was compared to a reduced fat, micronutrient rich, control formula, failed to show an advantage of IMN (18,28).

The use of a control formula identical to IMN in every respect, except the key nutrients in question, may be best from a basic-science standpoint. However, the pragmatic comparison of IMN to a standard reduced-fat, high-protein, antioxidant-rich feeding is often the most pertinent to the clinician. Immunonutri-

tion formulas, on average, are 5 times more expensive than the high-protein micronutrient-rich formulas used in most intensive care units. One group has demonstrated that in populations where use of IMN has significantly improved outcomes, there is unquestionable cost-effectiveness (37). However, in studies where the control feeding was a relatively inexpensive, reduced-fat, micronutrient-rich enteral formula and no outcome advantage was demonstrated with IMN (18, 28), the use of IMN would not be expected to be cost effective.

OTHER CONSIDERATIONS

The available data is consistent with a dose-dependent effect of arginine in IMN. Those studies that have reported improved outcomes in trauma, surgery and critical illness have all used IMN with arginine at or above 12 gm/1000 calories. A meta-analysis found that those studies with formulas containing a lower arginine content, did not have a reduction in infectious complications, but did report an increase in mortality (19); studies using high arginine IMN demonstrated a reduction in infections and no significant effect on mortality.

There is data that supports an interaction between fatty acids and arginine. In-vitro studies have demonstrated that omega-6 fatty acids increase arginase-I expression, while omega-3 fatty acids decrease arginase-I expression (46). A recent randomized human study confirms the in-vitro results by demonstrating that increased consumption of omega-3 fatty acids (food or supplement) significantly increased serum levels of L-arginine compared to placebo (47). The significance of this, if any, in terms of outcome in patients receiving arginine-containing IMN with or without fish oils remains to be determined.

One of the most controversial aspects of IMN formulas is that they provide a number of different nutrients at the same time. It is unclear if it is necessary to add all of the nutrients used in commercial IMN formulas for optimum reduction of infectious complications. There are few trials where the immunonutrients are the only variable that is different between the experimental and control formula. The current studies are inadequate to determine which nutrient combination, and at what dose, will optimize patient outcome. It is possible that some nutrients have positive effects while others have neutral or even negative effects, and that this may vary depending on the population and the severity of illness.

There remains a need for well-controlled studies to determine the ideal composition and dose of nutrients that will provide the best outcome for patients. Tests of single nutrients compared to multiple nutrients are required to determine:

- the "immunonutrition mix" that provides the best outcome,
- which nutrients are unnecessary,
- or perhaps, those nutrients that might even prove harmful.

Future trials should consider administering the specialized nutrients at scheduled times separate from the enteral feeding so that full doses of the immunonutrients may be provided regardless of formula volume.

Glucose Control

One cannot ignore the fact that most of the current IMN studies predate the data supporting aggressive glucose control in ICU settings (48). It is unclear if the reduction in infections realized with strict insulin-drip protocols has the potential to affect findings from IMN studies. It may be difficult to recognize any reduction in infectious complications from an IMN formula in a population where the baseline rate of infections is very low. However, removing other confounding factors that influence the rate of infections, such as proper glucose control, may allow the true benefit (or lack thereof) from IMN to become apparent in randomized studies.

CONCLUSIONS

Writing a first-class review article on IMN is a bit like writing a good article on how to make a silk purse from a sow's ear—the material you are given is not of a high enough quality to do an adequate job. This is in no way meant to insult the sow, or in this case, the concept of IMN. It is simply that the quality and size of the research is inadequate to answer the question. It is also clear that meta-analysis combining studies from 5 sub-

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stantially different IMN products, and each study with a different "dose" (amount received) of IMN and different type of control formula, does not provide definitive answers. Meta-analysis has actually provided the most potent data that not all arginine-containing IMN have the same results, and that it is inappropriate to consider all arginine-containing formulas as the same entity.

There is consistent data that those IMN formulas with an arginine content below 12 gm per 1000 calories, do not result in a reduction in infectious complications or length of stay, and may actually increase mortality in septic patients. This is confirmed by two recent studies. The use of low-arginine IMN did not show improvements in outcome in a heterogeneous ICU population compared to control tube feedings (43). Provision of low-arginine IMN in a septic population resulted in increased mortality compared to TPN (44). In contrast, those studies that have provided IMN formulas with at least 12 gm arginine/1000 calories, and that have provided reasonable amounts of nutrition (16,24,36), have demonstrated significant outcome improvements with significantly decreased mortality in at least one study (16).

However, this is not meant as a wholesale endorsement of those formulas with an increased arginine content. It remains unclear which component of IMN contributes to decreased infections and improved outcomes. It is entirely possible that some of the immunonutrients may have a negative effect that is masked by beneficial effects of other nutrients. There is a clear need for systematic research that will answer these questions. The possibility that some patient populations may be compromised by these formulas, while others are helped, also needs to be investigated in a systematic manner.

In the absence of definitive research data it would seem prudent to avoid low IMN with less than 12 gm arginine/1000 calories in septic patients, or those at significant risk of sepsis. There does appear to be adequate outcome and cost-effectiveness data to support the use of perioperative IMN containing >12 gm arginine/1000 calories, marine oils, and nucleotides in patients undergoing surgery for gastrointestinal cancer. There is a need for further studies in general ICU or septic patients before routine use in these populations can be endorsed. ■

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